Attachment 1

Declaration of Michael D. Laufer, M.D., Under 37 C.F.R. 1.132

Docket No.: 649218008US
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: MICHAEL D. LAUFER	
APPLICATION NO.: 10/810,276	CONFIRMATION NO.: 8525
FILED: MARCH 26, 2004	ART UNIT: 3735
FOR: METHOD FOR TREATING AIRWAYS IN THE LUNG	EXAMINER: D. M. SHAY

Declaration of Michael D. Laufer, M.D., Under 37 C.F.R. 1.132

I, Michael D. Laufer, M.D., hereby declare and state.

1. I received a Bachelor of Arts degree from the University of Colorado at Boulder in 1980, and I received a Medical Doctorate degree from the Stanford University School of Medicine in 1985. My postdoctoral training included the following positions: Intern in Emergency Medicine at Harbor-UCLA from 1985-1986; Resident in Emergency Medicine at Harbor-UCLA from 1986-1988; and Fellow/Attending in Trauma, Surgery, Emergency Medicine and Pre-Hospital Care at Stanford University from 1988-1989.

2. I hold the following licenses and certifications:

   1983 Advanced Cardiac Life Support Instructor and Provider
   1983 Basic Life Support Instructor and Provider
   1986 Advanced Trauma Life Support Provider and Course Instructor
   1986 Basic Trauma Life Support Instructor
   1986 Pediatric Advanced Life Support Provider and Instructor
   1987 Certified Base Station Physician for Los Angeles and Santa Clara Counties
   1992 Board Certified - American College of Emergency Medicine
   1993 Fellow - American College of Emergency Physicians
   1994 Board Certified Forensic Medical Examiner
   1995 Neonatal Advanced Life Support Provider
   1997 Fellow - American College of Forensic Medical Examiners

1997 Affiliate Faculty - Northern California Basic Trauma Life Support
1987 California Medical License No. G59661, DEA BL0859249
1990 Nevada Medical License No. 6566

3. I have also held and/or hold the following academic positions:

2006-present	Instructor at Harvard Medical School Beth Israel-Deaconesse Medical Center Department of Surgery
1990-present	Clinical Instructor at Stanford University
1990-1995	Assistant Clinical Professor at University of California San Francisco Department of Medicine
1989-1990	Acting Assistant Professor at Stanford University School of Medicine Department of Surgery/Emergency Medicine

4. Since 1993, I have been involved in creating new medical devices to treat patients with common illnesses, and I have started more than 10 companies directed to over 15 new technologies. In 1997, I founded Broncus Technologies, Inc., and Asthmatx, Inc. became a separate company from Broncus Technologies, Inc. in December of 2003. I am currently a Board Member and a paid consultant for Asthmatx, Inc., and hold option and stock interest in Asthmatx, Inc.

5. With respect to the subject matter of U.S. Patent Application No. 10/810,276, a person of ordinary skill in the art has a Medical Doctorate degree and 6 or more years of experience in treating patients with chronic and/or acute asthma.

6. I have carefully reviewed James et al., *The Mechanics of Airway Narrowing in Asthma*, Amr. Rev. Respir. Dis. Volume 139:242-246 (1989) ("James"); U.S. Patent No. 5,574,059 ("Regunathan"); U.S. Patent No. 5,053,033 ("Clarke"); and International Publication No. WO 97/37715 ("Waksman").

7. James describes mechanics of airway narrowing in asthma patients. James teaches that the airway walls of asthma patients are thickened by

chronic inflammation and concludes that such thickening of the airway walls could be as important as smooth muscle shortening in determining the airway responsiveness of these patients. (James at Summary.) James indicates that the airways of the asthmatic patients showed infiltration with inflammatory cells, thickening of the basement membrane, mucous gland and goblet cell prominence, and partial occlusion of the lumen with mucus and cellular debris. (James at p. 243, col. 3.) In addition, James discloses marked folding of the epithelium in some airways with a prominent circular layer of muscle. (James at p. 243, col. 3 to 244, col. 1.) The increase in wall thickness, therefore, is not confined to the airway smooth muscle, but rather it also includes the submucosa and epithelium. (James at p. 245, col. 1.) James, for example, teaches that the chronic inflammatory process present in the airway wall in patients with asthma is associated with (a) cellular infiltration, (b) deposition of connective tissue, (c) goblet cell metaplasia of the epithelium, and (d) an inflammatory exudate containing mucus in the airway lumen in addition to hypertrophy of smooth muscle. (James at p. 246, col. 1.) James further teaches that an important feature of asthma treatments at that time was the rapid reversibility of airway obstruction with drugs that relax smooth muscle. (James at p. 245, col. 3.) According to James, bronchodilation does not need to be limited to reversal of excessive smooth muscle contraction, but rather reversing the muscle contraction can also be applied for non-excessive muscle contraction of thickened airway walls to increase airway caliber and lower the resistance to a similar degree. (James at p. 245, col. 3.) Based on these findings, James concludes that changes produced by chronic inflammatory processes can lead to excessive airway narrowing without excessive smooth muscle contraction such that the treatment of asthma should focus on (a) reversing the inflammatory changes in the airway wall and (b) relaxation of the airway smooth muscle. (James at p. 246, col. 1.) James, however, does not disclose anything with respect to causing a change in mucus gland cells.

8. Before the present invention, there were several teachings in the prior art that airway smooth muscle was of the utmost importance and was indispensable for respiration. (Macklin, C.C., *The Musculature of the Bronchi and Lungs*, Physiol. Rev. (1929) 9:1-60.) As set forth in Mitzner, W., *Airway Smooth Muscle The Appendix of the Lung*, American Journal of Critical Care Medicine, (2004) 169:787-790 ("Mitzner"), the early body of literature dating back over a 125 year period taught that airway smooth muscle had one or more functional purposes. Although Mitzner cites later articles as refuting some of the functional purposes of airway smooth muscle, Mitzner also points out that other listed functional purposes were still thought to be valid as late as 2004 (e.g., peristalsis to assist exhalation). Therefore, in 1998, a person of ordinary skill in the art would have understood that airway smooth muscle had a functional purpose and that airway smooth muscle cells should not be killed.

9. In 1998, the United States Food and Drug Administration also held the prevailing view of the time that airway smooth muscle was important for normal lung function. This was one reason why the United States Food and Drug Administration did not grant Asthmatx, Inc. approval to treat asthma in a human patient by debulking airway smooth muscle tissue until 2005. For example, in response to an Investigational Device Exemption application regarding Asthmatx's Alair System, the USFDA stated:

> Airway smooth muscle facilitates airway dilation as well as airway constriction. Of concern is that ablation of airway smooth muscle in small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway bronchospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

(USFDA Letter dated 16 February 2001 regarding IDE No. G010016 attached in redacted format.)

10. James does not teach or otherwise suggest debulking or reducing the mass of the airway smooth muscle to reverse inflammatory changes for treating asthma. First, James teaches that the increase in airway wall thickness associated with asthma is not confined to the airway smooth muscle, but rather inflammation of the submucosa and the epithelium also contribute to the increased airway wall thickness. Second, James does not teach any mechanism to reverse the inflammation of the airway wall. Third, as explained in Paragraph 8 above, a person of ordinary skill in the art in 1998 would have understood that destruction or removal of airway smooth muscle was controversial because the prevailing view at that time was that airway smooth muscle performed a functional purpose essential to normal lung function. Therefore, in 1998, a person skilled in the art would not understand James to mean that asthma should, or even could, be treated by debulking the airway smooth muscle.

11. James expressly teaches that the treatment of asthma should focus on reversing the inflammatory changes in the airway wall and relaxation of the airway smooth muscle. A person of ordinary skill in the art would understand that reversing inflammatory changes in the airway involves acute reversal of inflammation of the submucosa and epithelium as opposed to debulking the airway smooth muscle because (a) the prevailing view in 1998 was that airway smooth muscle had a functional purpose and therefore should not be killed, (b) debulking does not provide acute relief, and (c) pharmaceutical treatment of the epithelium may provide acute relief.

12. Regunathan discloses that vascular hyperplasia, i.e., the excessive proliferation and hypertrophy of vascular smooth muscle cells, is a major pathogenic mechanism contributing to vascular pathology in atherosclerosis, hypertension resulting from renal artery stenosis and other causes, restenosis of coronary and other arteries after coronary angioplasty, insertion of vascular stents, and other conditions.

(Regunathan at 1:17-27.) The invention of Regunathan is directed to a non-invasive method of inhibiting the initiation or progression of vascular hyperplasia and, in particular, to inhibiting proliferation of vascular smooth muscle cells. (Regunathan at 1:34-37.) Regunathan, more specifically, teaches a method of inhibiting the proliferation of vascular smooth muscle cells by administering a vascular smooth muscle cell anti-proliferative effective amount of an I_2 imidazoline receptor agonist. (Regunathan at 1:37-42.) Regunathan, however, does not disclose anything with respect to causing a change in mucus gland cells.

13. Clarke is directed toward inhibiting restenosis associated with angioplasty and teaches that intimal hyperplasia or proliferation of vascular smooth muscle cells is a major factor in restenosis. (Clarke at 1:1-5 and 1:41-43.) Clarke further teaches vascular smooth muscle cells enter their growth cycle 2-3 days after injury and the majority of the vascular smooth muscle cells cease to proliferate within 7 days after injury. (Clarke at 1:43-50.) Clarke indicates that the total number of smooth muscle cells reaches a peak about two weeks after injury and remains constant for up to one year; Clarke states this suggests that a reduction of the number of smooth muscle cells injured during angioplasty will reduce the likelihood of subsequent restenosis. (Clarke at 1:50-55.) To inhibit restenosis, Clarke teaches reducing the proliferation of additional vascular smooth muscle cells in the blood vessel walls at an angioplasty site by irradiating the angioplasty site with the appropriate radiation in the UV wavelength range. (Clarke at 2:39-44.) The irradiation kills a major portion of the injured smooth muscle cells in the media so that few, if any, smooth muscle cells remain in the angioplasty site to proliferate and cause restenosis. (Clarke at 5:1-9.) However, as shown in Figures 3B and 3C, the thickness of media is not reduced by the process. Clarke does not disclose anything with respect to causing a change in mucus gland cells.

14. Waksman discloses an apparatus for delivering radioactive treatment from a radionuclide to tissue that has been damaged. Waksman teaches that the healing process in response to an injury is an overgrowth of tissue caused by increased cell proliferation that renarrows the lumen. (Waksman at 1:17-20.) In particular, Waksman teaches applying radiation from a radionuclide to prevent or inhibit hyperplasia following a balloon angioplasty procedure. (Waksman at 5:13-18 and 6:19-25.) Waksman provides a long list of vascular applications and also a list of non-vascular applications, including the bronchi and lungs, in which his invention may be useful. (Waksman 5:18 - 6:5.) However, in all of the applications, Waksman's invention is directed toward treating an area that has been damaged by an earlier procedure by inhibiting the proliferation of additional cells. Waksman, moreover, does not disclose anything with respect to causing a change in mucus gland cells.

15. In 1998, as well as now, a person of ordinary skill in the art would have understood that the purpose of both Regunathan, Clarke and Waksman was to inhibit injured vascular smooth muscle cells from producing additional vascular smooth muscle cells that would normally occur in response to damage, injury or other trauma to the vessel wall. With respect to vascular structures, restenosis is caused by hyperplasia as opposed to hypertrophy of smooth muscle cells. Hyperplasia in vascular applications is the excessive proliferation of new or additional cells above the level of normal cell production, whereas hypertrophy is the increase in tissue size caused by the filling with connective and scar tissue without necessarily increasing the number of smooth muscle cells above normal levels. A person of ordinary skill in the art would accordingly understand that Regunathan, Clarke and Waksman are limited to methods for reducing or inhibiting injured vascular smooth cells from producing additional smooth muscle cells to prevent hyperplasia.

16. Additionally, to a person of ordinary skill in the art, neither Regunathan nor Clarke nor Waksman teaches debulking or otherwise removing uninjured vascular smooth muscle tissue that existed before the injury occurred. First, Regunathan, Clarke and Waksman are all clear that hyperplasia (i.e., an increase in the number of cells) as opposed to hypertrophy (i.e., an increase in tissue size caused by the filling with connective and scar tissue) causes restenosis. Second, Regunathan, Clarke and Waksman teach methods for inhibiting the production of additional smooth muscle cells, but neither reference discloses debulking uninjured smooth muscle tissue that existed before injuring the vessel. Third, vascular smooth muscle provides an essential function for maintaining blood pressure through vasoconstriction and vasodilation, and as such a person skilled in the art would not apply the methods taught in Regunathan, Clarke and/or Waksman in a manner that would debulk the existing vascular smooth muscle tissue. Therefore, without an injury or other condition that causes proliferation of the smooth muscle tissue, a person of ordinary skill in the art would not apply the methods taught by Clarke, Regunathan and/or Waksman to airway smooth muscle or any other smooth muscle tissue in the body.

17. On 10 June 1998, I filed the present application directed to radical methods for treating asthma. In one embodiment the method includes selecting an airway that has hypertrophied airway smooth muscle, and irradiating a length of the airway with a light source. The light source has a wavelength of about 240 nm to about 280 nm and an intensity that causes a change in the airway such that a thickness of the airway smooth muscle decreases and bronchoconstriction of the airway is reduced. Another embodiment of the method includes selecting an airway for treatment and irradiating a length of the airway with a light source. The light source of this embodiment has a wavelength of about 240 nm to about 280 nm and an intensity which causes a change in the airway mucus gland cells such that mucus secretions of the airway are reduced.

18. In an asthmatic lung, the increase in thickness of the airway smooth muscle is caused by hypertrophy - not hyperplasia. As such, the airway smooth muscle does not suffer from an abnormally high proliferation of additional cells, but rather it is the increase in size of the uninjured airway tissue that contributes to the increase in airway wall thickness. By debulking the airway smooth muscle as set forth in several embodiments of my invention, the mass of the airway smooth muscle is reduced so as to reduce the ability of the airway to contract. This directly contradicts the position that Clarke's method would be applied to an asthmatic lung in accordance with the claimed method to decrease hypertrophy.

19. A person of ordinary skill in the art would not irradiate an uninjured airway wall of an asthmatic lung at a wavelength and intensity that, over time, would debulk airway smooth muscle based on the teachings of James, Regunathan, Clarke or Waksman, either individually or collectively. Clarke teaches applying the UV radiation in a manner that kills a portion of the injured smooth muscle cells to prevent or inhibit additional smooth muscle cells from proliferating. Clarke, in effect, proactively kills injured smooth muscle cells before their growth cycle to prevent the proliferation of additional cells. However, as explained above in Paragraph 16, without an injury or other condition that causes proliferation of smooth muscle cells, there is no reason to apply Clarke's method to airway smooth muscle or any other smooth muscle. Clarke accordingly does not teach debulking the smooth muscle cells, and a person of ordinary skill in the art would not apply Clarke in a manner that would cause such debulking because, at least in part, vascular smooth muscle provides an essential function for maintaining blood pressure. Regunathan and Waksman similarly teaches inhibiting proliferation of smooth muscle cells as opposed to debulking the smooth muscle tissue. Lastly, James does not teach debulking the airway smooth muscle, and a person of ordinary skill in the art in 1998 would not understand James to mean that asthma should, or even could, be treated by debulking the airway smooth muscle. Unlike the

cited references that are directed to preventing the proliferation of smooth muscle cells, several embodiments of my treatment seek to debulk existing uninjured airway smooth muscle affected by hypertrophy to provide a cure for chronic conditions. Therefore, it would not have been obvious to a person of ordinary skill in the art at the time of the invention to use the method of Clarke to treat asthma in light of the teachings of Regunathan, Waksman and James.

20. Additionally, even if Clarke's method was applied to an asthmatic airway, it would not result in debulking of the airway smooth muscle tissue. Vascular structures and airway structures are significantly different such that Clarke's method would be ineffective for debulking airway smooth muscle. Unlike the smooth lining of the endothelium in blood vessels, the epithelium in asthmatic airways has several folds (see, e.g., Figure 1 of filed application). Clarke teaches applying the UV radiation at a relatively low angle to the lumen wall that would result in shadowing within the airway such that some of the airway smooth muscle would not be treated, or at least not sufficiently treated, for debulking. The airway epithelium, which is comprised of tight junctions of columnar cells, is 10-15 times thicker than the single flat layer of squamous cells that comprise the vascular endothelium. Further, the airway epithelium necessarily facilitates diffusion of nitrogen for proper lung function while the endothelium prevents nitrogen diffusion and nitrogen-containing substances, and nitrogen monoxide in particular, which has a direct affect on causing vascular smooth muscle to contract, which could be catastrophic in an airway. The airway epithelium and blood vessel endothelium are accordingly two different materials with different properties that react differently to irradiation. As a result, a person of ordinary skill in the art would understand that the intensity level of Clarke's UV radiation to treat restenosis in a blood vessel would not likely be sufficient to debulk airway smooth muscle through the epithelium of an airway.

21. Also, a person of ordinary skill in the art would not be motivated or otherwise think of applying radiation to effect a change in the airway mucus gland cells such that mucus secretions of the airway are reduced based on James, Regunathan, Clarke, Waksman and/or the knowledge of a person of ordinary skill in the art at the time of the invention. Regunathan, Clarke and Waksman are all directed to treating portions of the vasculature that have been damaged by earlier medical procedures to inhibit or prevent the proliferation of additional smooth muscle cells. Nothing in these references teaches that mucus gland cells should or even could be changed. The vasculature, moreover, does not even have mucus gland cells such that there is no reason to believe that the methods taught by Regunathan, Clarke and/or Waksman have any application to airway mucus gland cells. Therefore, a person of ordinary skill in the art would not be motivated or otherwise think of applying radiation according to Clarke or Waksman to effect a change in the airway mucus gland cells such that mucus secretions of the airway are reduced.

22. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

7/21/2008
Date

Michael D. Lauer, M.D.

Attachment 1a

USFDA Letter dated 16 February 2001, regarding IDE No. G010016

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB 16 2001

Mr. Timothy R. Williams
Director of Regulatory and Clinical Affairs
Broncus Technologies, Inc.
1400 N. Shoreline Boulevard Bldg. A, Suite 8
Mountain View, CA 94043

Re: IDE Number G010016
Alair System
Dated: January 17, 2001
Received: January 18, 2001

Dear Mr. Williams:

The Food and Drug Administration (FDA) has reviewed your investigational device exemptions (IDE) application. We regret to inform you that your application is disapproved and you may not begin your investigation. Please be advised that, based on the data that you have provided, we believe that studies in humans pose significant potential risks that appear to outweigh the potential benefits. Our disapproval is based on the following deficiencies:

1. You provided pre-clinical data using the canine model. In total, there were nine animal studies performed to support this IDE application, with a total of 37 canines treated and over 2300 device activations.

   You have also provided the results of data collected outside of the United States (OUS) trial where one lobe was treated in 8 patients, 1 to 3 weeks before a scheduled lobectomy. There were 3 to 9 activations in each patient, for a total of 41 activations.

Even if normal healing of the larger treated bronchi were to occur, there are significant concerns that the underlying condition (asthma) would nonetheless remain. Airway smooth muscle facilitates airway dilation as well as airway constriction. Of concern is that ablation of airway smooth muscle in small bronchi may have negative effects by preventing airway dilation during sympathetic stimulation, e.g., during exercise. Patients could conceivably continue to have asthma attacks with secretions and smaller airway bronchospasm and then be unable to effectively cough and clear these secretions due to lack of larger airway smooth muscle tone. Reduced smooth muscle support of the conducting airways, coupled with underlying asthma, could lead to complications such as bronchiectasis.

If you submit information correcting the deficiencies, we will reevaluate your application. The information should be identified as an IDE amendment referencing the IDE number above, and must be submitted in triplicate to:

IDE Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, MD 20850

Alternatively, you may request a regulatory hearing regarding the disapproval of your IDE application. The enclosure "Procedures to Request a Regulatory Hearing" describes how to submit such a request. The procedures governing a regulatory hearing are described in the regulations at 21 CFR Part 16.

If you prefer not to request a regulatory hearing, you may nevertheless request that this decision be reviewed by the IDE Review Committee within the Office of Device Evaluation (ODE). The enclosure entitled, "IDE Review Committee and Procedures to Request Review" discusses the purpose and operation of the Committee as well as how to submit such a request to the Committee.

If you have any questions, please contact Frank Lacy at (301) 443-8517 ext-170.

Sincerely yours,

James E. Dillard III
Director
Division of Cardiovascular and
Respiratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures
(1) Procedures to Request a Regulatory Hearing
(2) IDE Review Committee and Procedures to Request Review